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UNITED S[redacted] DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	11

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No	Applicant(s)
09/132,521	Nagal et al.
Examiner	**Group Art Unit**
Stroup, Carrie	1633

X Responsive to communication(s) filed on *Jun 9, 2000*

This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

X Claim(s) *1-12, 14, and 15* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

__ Claim(s) _____ is/are allowed.

X Claim(s) *1-12, 14, and 15* is/are rejected.

__ Claim(s) _____ is/are objected to.

__ Claims _____ are subject to restriction or election requirement.

Application Papers

__ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

__ The drawing(s) filed on _____ is/are objected to by the Examiner.

__ The proposed drawing correction, filed on _____ is __ approved __ disapproved.

__ The specification is objected to by the Examiner.

__ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

__ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

__ All __ Some* __ None of the CERTIFIED copies of the priority documents have been

__ received.

__ received in Application No. (Series Code/Serial Number) _____.

__ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

__ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's amendment, Paper 14, filed 6/9/00, has been entered. Claims 1, 6, and 9-15 have been amended. Claims 1-12, 14, and 15 are currently pending in the present application.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 9 remains rejected, and claims 10, 11, 12, and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant's arguments filed 6/9/00 have been fully considered but they are not persuasive.

Applicant's claimed invention is to a method of treating HIV comprising administering to human subjects a recombinant Sendai virus vector expressing a substantial amount of biologically active CXC-chemokine for expression in vivo (claim 9); collecting target cells from human subjects, infecting the cells with a recombinant Sendai virus vector expressing a substantial amount of biologically active CXC-chemokine, and giving the infected cells back to the human subjects (claim 10); a *pharmaceutical* composition comprising a recombinant Sendai virus vector encoding a stromal cell-derived factor (claims 11 and 12); incubating a host cell transfected with said vector *in vitro* to allow secretion of a substantial amount of biologically active chemokine; and contacting said chemokine with cells *(in vivo)* that are infected with HIV (claim 15).

The Office maintains that the specification fail to provide an enabling disclosure for *in vivo* gene therapy utilizing a recombinant Sendai virus vector encoding a chemokine for the treatment of HIV (claim 9). After further review of the specification, it has also been determined that the specification also fails to provide an enabling disclosure for a method of conducting *ex vivo* gene therapy utilizing the claimed SeV encoding a chemokine (claim 10).

The Applicant states in Paper 14, filed 6/9/00, that the requirement by the Examiner for the practice of the full scope of the claimed invention to be enabled by the pending specification is overbroad, and in conflict with *In re Wands*, because the Applicant has meet the enablement requirement for *in vivo* gene therapy by disclosing the identity of chemokines having anti-HIV activity, the identity of a recombinant viral vector capable of delivering biologically active chemokine to a mammalian host cell, while also providing examples of Sendai virus vectors for use in the present invention, DNA constructs and construction of rSeV, regulation of chemokine gene expression within SeV, modification of the Sendai virus to maintain or improve the vector's expression capability, safety, or efficiency of transcription and replication, generation of nondisseminative SeV, generation of rSeV in vitro and in vivo, intended cell types, production of chemokines in mammalian cells, clinical application, pharmaceutical carrier for administration, determination of dose for administration, and determination of chemokine biological activity chemotaxis and anti-HIV activity (Paper 14, page 5-8). It is noted that these cited teachings by the Applicant of a disclosure within the specification are in fact variables or modifications that the artisan must consider in ensuring that a high enough level of SDF-1α expression occurs in HIV infected tissue and blood so as to have any therapeutic effect, or they are merely explanations on the actual structure of the exemplified vector (e.g, regulation of gene expression pg 5, lines 22-31). Said variables or modifications, such as the use of hybrid liposomes-SeV (e.g., modfication of SeV to improve expression, pg 5, lines 32-pg 6, line 18), require extensive alterations of the claimed invention the essential teachings of which are not disclosed within the specification.

The Applicant has still not demonstrated nor convincingly argued that the claimed vector has the ability to express a therapeutically sufficient level of a chemokine for use in *in vivo* or *ex vivo* gene therapy. In fact it was only the exemplified pSeVSDF-1α transfected into chicken embryo fibroblasts which demonstrated the production of 10μg/ml *in vitro* after 72 hours of incubation, wherein Moriya et al (*FEBS Letters*, 1998, 425: 105-111) disclose that the use of this specific cell type elicited the highest level of transgene expression as compared to the other cells types tested, e.g., CV1 (pg 109, para. 3.2). The specification has not demonstrated, nor would one of skill in the art expect such a high level of expression in the other cells types disclosed by the specification, such as human PBMC (pg 7, last para.). Therefore, the dose per route of administration for use with the claimed invention is undetermined, and cannot be easily assessed by the skilled artisan because the specification does not disclose measurements on the use of the claimed vector with any cell type which would realistically be transfected *in vivo*, or even used for *ex vivo* gene therapy. To utilize the claimed invention for gene therapy, the artisan would still be required to practice undue experimentation to determine the amount of SDF-1α expressed from each cell type, and the appropriate modifications which may be required to increase the level of expression such that any therapeutic benefit in the treatment of HIV would occur for gene therapy.

Additionally, the specification does not disclose targeted delivery of the disclosed SeVSDF-1α to any cell type *in vivo*. The Applicant states in Paper 14, page 8, that " the skilled artisan would recognize that the recombinant Sendai virus of the present invention may be suspended in a saline solution and injected directly into a lymph node of a patient infected with HIV to achieve delivery to CD4 T-cells residing in the lymph nodes." The mere injection of a pharmaceutical solution comprising the disclosed pSeVSDF-1α does not ensure the efficient transfection *in vivo* of any cell type. Is the Applicant suggesting that the vector will transfect CD4 T-cells, express the SDF-1α protein, and then secret it so that it may inhibit HIV membrane fusion to the same cell or neighboring cells? If so, what level of expression of SDF-1α would occur? Applicant's are reminded that the art of targeted delivery does not consist merely

of getting the vector to the proper location within the subject, but also refers to the tropism of the vector and its specificity in infecting the desired cell type while not infecting others (e.g., Miller et al, Figure 1, pg 191; see entire article).

While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

It is reiterated, though, that the pending application is void of any teachings on the method of targeted delivery of a vector *in vivo*, resulting in undue experimentation by one of skill in the art to have the pSeVSDF-1 reach HIV infected tissue and blood at a sufficiently high enough concentration so as to have any therapeutic effect.

The Applicant asserts that the specification meets the requirements of *In re Wands*, which permits a considerable amount of experimentation if it is merely routine (Paper 14, page 10). Applicants are reminded that the courts have addressed this situation in Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997):

> "...that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."

Furthermore, as stated in the ruling for Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991) "It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims". As previously noted in Paper 5, filed 4/14/99, page 3, and Paper 9, filed 10/20/99, page 3, *in vivo* gene therapy is widely accepted within the scientific/medical community to be a highly unpredictable art. Likewise, *ex vivo* gene therapy is also consider highly unpredictable. For example, Verma et al (*Nature*, 18 Sept 1997, 389: 239-242) states that "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (pg 239, col. 1, para. 2). Therefore, contrary to Applicant's assertion that the specification discloses at least one operable embodiment (Paper 14, pg 13), the Office maintains that this is in fact not the case because the specification has only provided a method of recombinantly producing a biologically active SDF-1 *in vitro* at a high yield and not the use of SeV in a method of treatment. Therefore, it is maintained that in the absence of a sufficient disclosure on the

appropriate cell for transfection with the SeVSDF-1 vector and methods of targeted delivery in vivo, then one of skill in the art would be required to practice undue experimentation to utilize the claimed invention for the treatment of HIV in a human subject in either an *in vivo* or ex vivo method of gene therapy.

It has also been determined that the specification fails to provide an enabling disclosure for a method of conducting protein therapy (claim 15) because the specification is void of methods of administering a recombinantly derived SDF-1 to a subject to include dosing regime and route of administration such that any therapeutically effective treatment of HIV would be expected to occur. Lastly, in light of the fact the specification fails to provide an enabling disclosure for the use of any method of treatment in a human subject (e.g, claims 9, 10, 15), then it has also been determined that the specification is not enabling for a composition with an intended use as a pharmaceutical.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4. Claims 1-8, 11, 12, 14, and 15 are rejected under 35 U.S.C. 102(a) as being anticipated by Moriya et al (3/1998).

Applicants' claimed invention is to a Sendai virus expressing a chemokine, such as CXC stromal cell-derived factor alpha or beta, wherein the vector is disseminative or is infectious and replicates autonomously, but is not disseminative (claims 1-5); a method of producing a chemokine via inserting at least one chemokine gene into a

Sendai virus vector, and recovering said chemokine via centrifugation (claims 6-8); and a pharmaceutical composition comprising a recombinant Sendai virus vector expressing stromal cell-derived factor alpha or beta, wherein said vector is disseminative or non-disseminative (claims 11 and 12); and a host cell transfected with a recombinant Sendai virus vector expressing a substantial amount of biologically active chemokine and the use of such in a method of inhibiting HIV proliferation by incubating said cell *in vitro* to allow secretion of said chemokine and contacting said chemokines *in vitro* to cells that are infected with HIV (claims 14 and 15).

Moriya et al disclose recombinant Sendai viral vector encoding stromal cell-derived factor alpha or beta which was transfected into chicken embryo fibroblasts wherein culture supernatants of said cells were centrifuged at 48,000xg for 1hr to remove SeV/SDF-1α orβ and the amount of biologically active SDF-1α reached 10μg/ml in a 72 hour incubation. Said SDF-1α was then successfully used to suppress replication of three T cell line tropic HIV-1 strains in culture by inhibiting membrane fusion (see entire article). Therefore, the claimed invention was clearly anticipated.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-8, 11, 12, 14, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et al (1997) in view of Bleul et al (1996).

Applicants' claimed invention is to a Sendai virus expressing a chemokine, such as CXC stromal cell-derived factor alpha or beta, wherein the vector is disseminative or is infectious and replicates autonomously, but is not disseminative (claims 1-5); a method of producing a chemokine via inserting at least one chemokine gene into a Sendai virus vector, and recovering said chemokine via centrifugation (claims 6-8); and a pharmaceutical composition comprising a recombinant Sendai virus vector expressing stromal cell-derived factor alpha or beta, wherein said vector is disseminative or non disseminative (claims 11 and 12); and a host cell transfected with a recombinant Sendai virus vector expressing a substantial amount of biologically active chemokine and the use of such in a method of inhibiting HIV proliferation by incubating said cell *in vitro* to allow secretion of said chemokine and contacting said chemokines *in vitro* to cells that are infected with HIV (claims 14 and 15).

Yu et al teach the use of a Sendai viral vector to express gp120, wherein the V(+) vector version resulted in 2.2μg/10^6 infected cells and the V(-) version resulted in 6.0μg/10^6 infected cells, "a level that is the highest currently attainable for gp120 production in mammalian cells" (abstract), and wherein the gp120 was demonstrated to be biological active by its ability to bind to the surface of CD4-expressing MT4 cells (pg 461, col. 1, para. 2). The virions were also recovered via centrifugation at 40,000*g. Yu et al does not teach the use of the SeV to express a chemokine.

Bleul et al teach that the chemokine SDF-1 inhibits the infection of HeLa-CD4 cells, CXCR-4 transfectants, and peripheral blood mononuclear cells ty the T-trophic HIV strain.

In light of Yu and Bleul et al, it would have been obvious to one of ordinary skill in the art to use the SeV vector disclosed by Yu to express SDF-1 in vitro. One would have been motivated to do this to yield a high volume of biologically active SDF-1 which could then be used for protein therapy in the treatment of HIV.

The Applicant states in Paper 14, filed 6/9/00, that Yu et al does not disclose or suggest the use a Sendai virus system used to express large quantities of a chemokine that maintains its biological activity. The Applicant is

referred to the citation above for Yu et al. Additionally, the Applicant states that Yu et al teach away from this concept by stating that "no definite assessment of the utility of the SeV vector has been made because of the inactivation of the enzyme activity due to extensive aggregation of the expressed luciferase molecules in cells" (Paper 14, pages 15-16). It is noted that Yu et al is referring to the use of the SeV vector to express biologically active luciferase, wherein they had already shown the use of the SeV vector to express biologically active gp120. It is a characteristic of the luciferase protein that it aggregates and becomes biologically inactive, and not due to the vector itself. The Offices notes that the passage from Yu et al as referenced by the Applicant actually reads:

> "...Thus, our SeV technology should be widely applicable without difficulty as long as one follows the above guidelines for maximizing the recovery rate of the progeny. After the completion of this work on HIV-1 gp120, the same strategy has indeed allowed our group to express the firefly luciferase gene (Hasan et al, 1997). **In this case, however**, no definite assessment of the utility of the SeV vector has been made because of inactivation of the enzyme activity due to extensive aggregation of the expressed luciferase molecules in cells." (Yu et al, pg 463, col. 2, para. 2)

Therefore, in light of Yu et al, one of ordinary skill in the art would expect that use of the SeV vector to encode a chemokine would result in a biologically active protein which did not aggregate.

No claim is currently allowed. The Applicant is encouraged to amend the claims to differentiate the specific construct design and method of making of such from the art (Yu et al).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-0294.

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